PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MBUS 1677 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/005394	International filing date *(day/month/year)* 17.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC C07D311/80		
Applicant JOHNSON MATTHEY PUBLIC LIMITED COMPANY		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.07.2005	06.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-8510

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005394

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

3-9	as originally filed
1, 2	received on 20.07.2005 with letter of 18.07.2005

Claims, Numbers

1-12	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: US 2003/050334
D2: US-B1-6 403 126
D3: SHULAMIT ET AL.: "Resolution of chiral cannabinoids on amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase: effects of structural features and mobile phase additives" JOURNAL OF CHROMATOGRAPHY, vol. 654, 1993, pages 53-54, XP002324648

1.1) Amendments

The amendments filed with letter dated 18 July 2005 do not introduce any subject-matter which extends beyond the content of the application as originally filed, so as to comply with the requirements of Articles 19(2) and 34(2b) PCT.
The Applicant deleted a paragraph on page 1, line 34 until page 2, line 4 of the previous description pages.

2) Novelty (Reference to section V)

D1 and D2 disclose processes for the supercritical extraction of Δ^9-tetrahydrocannabinol (Δ^9-THC) with chromatographic methods and wherein the solvent used is carbon dioxide (cf. D1 on page 2 and D2 on columns 2 and 3).
No mention that the stationary phase comprises a derivatised polysaccharide has been found.

D3 describes the resolution of some chiral cannabinoids on amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase; however, carbon dioxide does not seem to have been used in the mobile phase.

Thus, the subject-matter of present claims 1-12 appears to meet the requirements of Article 33(3) PCT.

3) Inventive step (Reference to section V)

D1, which may be considered to represent the closest state of the art, discloses a process for the supercritical extraction of Δ^9-THC and uses carbon dioxide as supercritical fluid.

D1 therefore differs from the subject-matter of the present application in the absence of a derivatised polysaccharide in the stationary phase.
The problem to be solved by the present application may thus be regarded as the provision of a further process for the production of enatiomerically pure (-)Δ^9-THC.
As already stated in paragraph 2 above, D3 reports the resolution of some chiral cannabinoids on amylose tris(3,5-dimethylphenylcarbamate) chiral stationary phase, and on page 63, right-hand column of D3, it is stated that the chromatographic system disclosed in said document is capable of assessing an enantiomeric excess of the cannabinoids of $\geq$99.9% (cf. also page 59, right-hand column, first and second lines).
Moreover on page 56, right-hand column D3 mentions that "apart from the two enantiomers of Δ^6-THC, all the enantiomeric pairs could be easily separated using various percentages of 2-propanol in the mobile phase".
Accordingly, the skilled person, when trying to solve the cited technical problem, would obviously combine the teaching of D1 with that of D3 in order to arrive at the present subject-matter, and reasonably expect that also the new process leads to good results.

Consequently, the subject-matter of present claims 1-12 does not seem to meet the criteria of Article 33(3) PCT.

The Examiner cannot agree with the Applicant's arguments set forth with letter dated 18 July 2005 as the present inventive step objection is based on the teaching of documents D1 and D3; the Applicant, however, seems to have understood that said objection was based on the combination of D1 with D2.
Moreover, it is not clear why the Applicant deleted the last passage on page 1 of the description; although that passage did not constitute any relevant subject-matter which was important for the definition of the invention, it appeared from there that the Applicant considered D2 as describing a process for preparing (-)Δ^9-THC from marijuana by using a preparative preparation, namely "a chromatographic process wherein the eluent is a supercritical fluid such as carbon dioxide with or without an organic solvent modifier".
Said lines are in contradiction with what the Applicant wrote on 18 July 2005, namely that D2 does not disclose any preparative separation process comprising a chromatographic step wherein carbon dioxide is in the mobile phase.

4) Further observations (Reference to section VIII)

The subject-matter of claim 11 does not appear to be supported by the description.

PROCESS FOR PURIFYING (-)-Δ^9-TRANS-TETRAHYDROCANNABINOL

The present invention relates to a process for purifying (-)-Δ^9-trans-tetrahydrocannabinol. The compound is separated from a mixture of cannabinoids using a chromatographic technique.

(-)-Δ^9-trans-tetrahydrocannabinol is the active ingredient in marijuana. It is used therapeutically as an inhalant or an oral drug for stimulation of appetite among AIDS and cancer chemotherapy patients. Tetrahydrocannabinols (THCs) can be isolated from marijuana (a mixture of leaves and flowering heads of the plant *Cannabis Sativa*). Alternatively, THCs can be obtained by synthetic routes, e.g. as described in WO 02/096899. Enantiomerically pure THCs are required for formulation into drug products, but the purification of THCs, whether produced by isolation or synthesis, is challenging. The present inventors have sought to provide a process for providing enantiomerically pure (-)-Δ^9-trans-tetrahydrocannabinol ((-)-Δ^9-THC).

Chromatographic techniques have been used to separate (-)-Δ^9-THC from other cannabinoid compounds. The identification of cannabis products in drug samples has been achieved using Supercritical Fluid Chromatography. Such methods are described by Bäckström et al (Science & Justice, 1997, 37(2), 91-97), Cole ("Analysis of Cannabis by Supercritical Fluid Chromatography with Ultraviolet Detection", pages 145-148 in "Supercritical Fluid Methods and Protocols" ed. by Williams and Clifford), Veress (Journal of Chromatography A, 668 (1994), 285-291) and Later et al (Journal of Chromatographic Science, 1986, 24, 249-253). In these methods, very small samples (typically µg amounts) are analysed and the (-)-Δ^9-THC is often destroyed during the detection step (e.g. by flame ionisation detection or by chemical ionisation mass spectrometry). These chromatographic methods achieve separation of (-)-Δ^9-THC from other cannabinoid compounds, but are completely unsuitable for preparing sufficient quantities of enantiomerically pure (-)-Δ^9-THC for incorporation into pharmaceutical products.

Levin et al (Journal of Chromatography A, 654 (1993), 53-64) have developed an analytical procedure for separating enantiomeric mixtures of cannabinoid compounds. The chromatographic method uses a Daicel Chiralpak ® AD column, which is based on amylose tris(3,5-dimethylcarbamate) supported on macroporous silica gel. The mobile phase is n-hexane with ethanol or propanol. The enantioselective analysis determines the optical purity of samples but does not provide useful quantities of separated enantiomers.

Although chromatographic procedures have been used to analyse samples of cannabinoid compounds, an effective preparative separation of enantiomerically pure (-)-Δ^9-THC has not been demonstrated. The present inventors have devised a chromatographic process that can be used to prepare quantities of enantiomerically pure (-)-Δ^9-THC for incorporation into pharmaceutical products.

Accordingly, the present invention provides a preparative separation process wherein (-)-Δ^9-trans-tetrahydrocannabinol is separated from a mixture of cannabinoids, wherein the process comprises at least one chromatographic step wherein a mobile phase passes through a stationary phase, characterised in that the stationary phase comprises a derivatised polysaccharide and the mobile phase comprises carbon dioxide.

The inventors have found that a chromatographic process combining a derivatised polysaccharide stationary phase and a carbon dioxide-containing mobile phase provides an effective preparative separation of (-)-Δ^9-THC. By "preparative separation process" we mean a process that is capable of providing at least 0.1g of purified product, preferably at least 1g of purified product in a reasonable timeframe, i.e. less than a day.

Preferably the mobile phase in the present invention is a mixture of carbon dioxide and one or more modifiers. The modifier can be any liquid solvent such as an